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BRIEF ARTICLE

Ku80 gene G-1401T promoter polymorphism and risk of gastric cancer

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Abstract

AIM: To evaluate the possible relationship between the *Ku80* gene polymorphism and the risk of gastric cancer in China.

METHODS: In this hospital-based case-control study of gastric cancer in Jiangsu Province, China, we investigated the association of the Ku80 G-1401T (rs828907) polymorphism with gastric cancer risk. A total of 241 patients with gastric cancer and 273 age- and sex-matched control subjects were genotyped and analyzed by polymerase chain reaction-restriction fragment length polymorphism.

RESULTS: The frequencies of genotypes GG, GT and TT were 65.6%, 22.8% and 11.6% in gastric cancer cases, respectively, and 75.8%, 17.6% and 6.6% in controls, respectively. There were significant differences between gastric cancer and control groups in the distribution of their genotypes (P = 0.03) and allelic frequencies (P = 0.002) in the Ku80 promoter G-1401T polymorphism.

CONCLUSION: The T allele of *Ku80* G-1401T may be associated with the development of gastric cancer.

Key words: *Ku80*; Gastric cancer; Polymorphism; Promoter; Carcinogenesis

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INTRODUCTION

Gastric cancer is one of the most frequent malignancies in many countries, accounting for 8.7% of all cancers and 10.4% of all cancer deaths in the year of 2000[1]. In China, gastric cancer remains the leading cause of cancer-related mortality among men and women[1,2]. It is estimated that about 39% of gastric cancer cases occur in Chinese population[1,2]. The environmental factors, diet, tobacco, alcohol and *Helicobacter pylori* infection are well-known causes of gastric cancer in China[3-5]. However, only a fraction of individuals exposed to these factors

develop gastric cancer, suggesting that individual susceptibility to gastric cancer should be different. Currently, the genomic etiology of gastric cancer is of great interest but largely unknown.

DNA damage drives the formation and development of malignant tumors that ameliorate this damage, and its sequelae can be categorized as either gatekeeper or caretaker tumor suppressors, depending on their mode of action[6]. Nonhomologous end joining (NHEJ) repairs DNA double-strand breaks (DSBs) by joining ends without using a homologous template strand and has been described as a caretaker[7,8]. Many studies have shown that NHEJ is the predominant repair system in humans, which included the DNA ligase IV and its associated protein XRCC4, and the three components of the DNA-dependent protein kinase (DNA-PK) complex, Ku70, Ku80, and the catalytic subunit PKcs[9]. The *Ku80* gene, also known as XRCC5, is an important and specific member of NHEJ. Ku70 and Ku80 form a heterodimer called Ku that is well known for its role in NHEJ pathway[10].

Ku acts as a regulator of transcription by interacting with the recombination signal binding protein Jκ and the nuclear factor (NF)-κB p50 homodimer to up-regulate p50 expression, which may regulate the proliferation of gastric cancer cells[11]. Gastric cancer cells with a low level of constitutive NF-κB had a lower expression level of Ku70 and Ku80, which was reflected in the lower nuclear levels of Ku proteins, than the wild-type cells and the cells transfected with control vector[12,13]. In addition, several studies reported that gastric cancer patients with a lower Ku80 expression level had a slightly prolonged survival after neoadjuvant chemotherapy[14-16].

Genetic polymorphisms in *Ku80* genes influence DNA repair capacity and change predisposition of several cancers, including colorectal[17], bladder[18] and oral cancers[19]. In addition, in these hospital-based case-control studies of other cancers, it was reported that the frequency of GT/TT type of the *Ku80* gene at promoter G-1401T (rs828907) was significantly higher in cases than in controls[17-19]. Thus, we assumed that the specific polymorphism of *Ku80* gene may also contribute to gastric cancer. To test the hypothesis that the promoter G-1401T polymorphism is associated with the risk of gastric cancer, we used polymerase chain reaction-restriction fragment length polymorphism (PCR-RELP) to genotype this polymorphism in a hospital-based case-control study of 241 patients with gastric cancer and 273 age- and sex-matched cancer-free controls. The results of this research will lead to a better understanding of the role of SNPs in the *Ku80* genes in gastric cancer carcinogenesis. Such knowledge may eventually lead to the development of better preventive measures for gastric cancer.

MATERIALS AND METHODS

Study population

The case-control study consisted of 241 patients with gastric cancer and 273 cancer-free control subjects. The gastric cancer patients were confirmed histologically. Genetically unrelated cancer-free individuals were recruited as controls who were selected by matching for age and gender during the same period. All subjects were Han Chinese from the eastern region of China and randomly selected from the Department of General Surgery of the First Affiliated Hospital of Nanjing Medical University between 2005 and 2009. All patients and control subjects voluntarily participated in the study, completed a self-administered questionnaire and donated 5 mL of blood samples. The questionnaire included questions on sex, age, residence, diabetes, hypertension and smoking status. Smoking was defined as ⩾ 10 cigarettes per day. This research protocol was approved by the Institutional Review Board of Nanjing Medical University.

Genotyping analysis

Genomic DNA was isolated from peripheral blood lymphocytes using standard phenol-chloroform extraction, as previously described[20,21]. PCR-RELP assay was used to type the *Ku80* G-1401T (rs828907) polymorphisms. In brief, the primers of the *Ku80* G-1401T polymorphism were 5'-TAGCTGACAACCTCACAGAT-3' (forward) and 5'-ATTCAGAGGTGCTCATAGAG-3' (reverse)[19], which generated a 252-bp fragment. The PCR reaction was performed in a total volume of 20 μL containing 2 μL 10 × PCR buffer, 1.25 mmol/L $MgCl_2$, 0.1 mmol/L dNTPs, 0.25 μmol/L each primer, 200 ng of genomic DNA and 1 U of *Taq* DNA polymerase (MBI Fermentas). The PCR was performed at 94℃ for 5 min and followed by 35 cycles of 30 s at 94℃, 30 s at 55℃ and 30 s at 72℃, with a final elongation at 72℃ for 10 min. The restriction enzyme *Bfa*I (New England BioLabs) was used to distinguish the PCR product, and the genotypes were discriminated on 3% agarose gel and visualized by staining with 0.5 μg/mL ethidium bromide. The wild-type G-allele produced a single 252-bp fragment, and the polymorphic T-allele produced 2 fragments of 81-bp and 171-bp. Approximately, 10%-15% of the samples were randomly selected for repeated assays, and the results were 100% concordant.

Statistical analysis

Continuous variables are presented as mean ± SD and compared by unpaired Student's *t* test. Continuous variables departing from the normal distribution were presented as median and interquartile range and analyzed by Mann-Whitney *U*-test. Discrete variables were represented as frequencies and percentages and evaluated by the Pearson's χ^2 test. Pearson's χ^2 test was also used to compare the distribution of the *Ku80* genotypes between cases and controls. The association between the *Ku80* G-1401T polymorphism and the risk of gastric cancer was estimated by odds ratio (OR) and 95% CI using multivariate logistic regression. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Table 1 Baseline characteristics of cases and controls *n* (%)

Characteristics	Cases (*n* = 241)	Controls (*n* = 273)	*P*
Sex (male)	181 (75.1)	193 (70.7)	0.43
Age (yr)	57.9 ± 12.9	56.9 ± 14.1	0.52
Smoking	61 (25.3)	39 (14.3)	0.014
Residence (rural)	111 (46.1)	142 (52.0)	0.32
Hypertension	21 (8.7)	28 (10.3)	0.58
Diabetes	15 (6.2)	22 (8.1)	0.51

Table 2 Genotype of *Ku80* G-1401T polymorphism in cases and controls *n* (%)

Genotype	Cases	Control
GG	158 (65.6)	207 (75.8)
GT	55 (22.8)	48 (17.6)
TT	28 (11.6)	18 (6.6)

χ^2 = 7.26, df = 2, *P* = 0.03.

RESULTS

Baseline characteristics

The frequency distributions of selected characteristics of the cases and controls are presented in Table 1. There was no significant difference between the cases and controls in sex (male: 75.1% *vs* 70.7%, *P* = 0.43) and age (57.9 ± 12.9 years *vs* 56.9 ± 14.1 years, *P* = 0.52), indicating that the matching for the subjects was successful. More smokers were found among gastric cancer cases compared with controls (25.3% *vs* 14.3%, *P* = 0.014). No significant differences were noted in residing in the rural area (46.1% *vs* 52.0%, *P* = 0.32), hypertension (8.7% *vs* 10.3%, *P* = 0.58) and diabetes (6.2% *vs* 8.1%, *P* = 0.51).

Genotype distributions and allele frequencies

Table 2 shows the distribution of the genotypic for the *Ku80* G-1401T (rs828907) between gastric cancer patients and controls. The genotypic frequencies in both gastric cancer and control groups were in agreement with those predicted by Hardy-Weinberg equilibrium (*P* = NS). The distribution of the *Ku80* G-1401T genotypes (GG, GT and TT) was markedly different between cases (65.6%, 22.8%, and 11.6%) and controls (75.8%, 17.6%, and 6.6%, *P* = 0.03). A significantly different distribution of the *Ku80* G-1401T genotype was demonstrated among the cases and controls. As shown in Table 3, the frequency of T allele was significantly higher in gastric cancer patients than in control subjects (23.0% *vs* 15.4%, *P* = 0.002).

Stratified analyses for the variant Ku80 genotype in cases and controls

The multivariate logistic regression analysis was further used to evaluate the association between the G-1401T polymorphism and gastric cancer stratified by risk factors including age, sex, smoking and residence under control (Table 4). Adjusted OR (for age, sex, smoking status, residence, diabetes and hypertension) with 95% CI for mutant genotypes was all described. In statistical analyses stratified by the median age of controls (58 years), the increased risk associated with the GT/TT genotypes tended to be more evident in the younger subjects aged < 58 years (adjusted OR = 1.97, 95% CI: 1.05-2.90). However, we did not note a statistically significant inverse association with gastric cancer risk in older subjects aged ⩾ 58 years (adjusted OR = 1.31, 95% CI: 0.88-1.96). The adjusted OR for the GT/GT genotypes was 1.81 (95% CI: 1.28-2.52) in male subjects and 1.33 (95% CI: 0.81-2.24) in female subjects. We did not note a statistically significant inverse association with gastric cancer risk in both non-smokers (adjusted OR = 1.48; 95% CI: 1.08-2.02) and smokers (adjusted OR = 2.52; 95% CI: 1.25-5.18). In urban subjects, there was significant evidence of an increased risk of gastric cancer in the variant genotypes (adjusted OR = 1.88; 95% CI: 1.26-2.76), while the association was not statistically significant in rural subjects (adjusted OR = 1.48; 95% CI: 0.99-2.15).

Table 3 Allele distribution of *Ku80* G-1401T polymorphism in cases and controls *n* (%)

Allele	Cases	Controls
G	371 (77.0)	462 (84.6)
T	111 (23.0)	84 (15.4)

χ^2 = 9.73, df = 1, *P* = 0.002.

DISCUSSION

In this hospital-based, case-control study, we assessed the potential association between the *Ku80* G-1401T polymorphism and the presence of gastric cancer in Chinese population. To our best knowledge, this is the first study linking the *Ku80* G-1401T polymorphism with gastric cancer risk. Our data showed that the *Ku80* -1401 G to T variant was associated with the increased risk of gastric cancer.

Gastric cancer is a genetic disease developing from a multifactorial, multigenetic and multistage process[22,23]. It was widely accepted that both genetic and environmental factors may be involved in the etiology of gastric cancer[24]. During the multistage carcinogenesis, Ku80 may be involved in multiple important cellular processes. To date, several studies have reported abnormal expression of Ku80 protein in various cancers[13,25-28]. Over-expression of Ku80 increased the capability of cancer acquired resistance to radiation and chemical drugs[29-31], while suppression of Ku80 expression decreased cellular proliferation, colony formation and inhibited tumorigenicity in a xenograft model[32]. As an important component of NHEJ, Ku80 and Ku70 form a heterodimer, which acts as a regulatory subunit of the DNA-dependent protein kinase complex DNA-PK by increasing the affinity of the catalytic subunit PRKDC to DNA[17]. The *Ku80* gene plays an important and specific role in removing DSBs. Chang *et al*[18]

Table 4 Stratification analyses of the association between Ku80 polymorphism and risk of gastric cancer *n* (%)

Variable	Cases (*n* = 241)		Controls (*n* = 273)		Adjusted OR (95% CI)[1]	*P*
	GG	GT + TT	GG	GT + TT		
Age (yr) (median)						
< 58	76 (62.3)	46 (37.7)	109 (76.8)	33 (23.2)	1.97 (1.05-2.90)	0.01
⩾ 58	82 (68.9)	37 (31.1)	98 (74.8)	33 (25.2)	1.31 (0.88-1.96)	0.3
Sex						
Male	118 (65.2)	63 (34.8)	149 (77.2)	44 (22.8)	1.81 (1.28-2.52)	0.01
Female	40 (66.7)	20 (33.3)	58 (72.5)	22 (27.5)	1.33 (0.81-2.24)	0.46
Smoking status						
Smokers	39 (63.9)	22 (36.1)	32 (82.1)	7 (17.9)	2.52 (1.25-5.18)	0.051
Non-smokers	119 (66.1)	61 (33.9)	175 (74.8)	59 (25.2)	1.48 (1.08-2.02)	0.054
Residence						
Urban	85 (65.4)	45 (34.6)	102 (77.7)	29 (22.3)	1.88 (1.26-2.76)	0.025
Rural	73 (65.8)	38 (34.2)	105 (73.9)	37 (26.1)	1.48 (0.99-2.15)	0.16

[1]Adjusted for age, sex, smoking status, hypertension, diabetes and residence.

found evidence that the *Ku80* G-1401T variant was associated with increased risk of bladder cancer in a central Taiwanese population. A recent study, involving 362 patients with colorectal cancer and 362 age- and gender-matched healthy controls, showed that the T allele *Ku80* G-1401T conferred a significantly (P = 0.0069) increased risk of colorectal cancer[17]. These observations were consistent with the findings previously described by other investigators from Asian populations[19].

To further investigate the association between the *Ku80* promoter G-1401T polymorphism and the risk of gastric cancer, we conducted this hospital-based case-control study in a Chinese population which incorporated the information on exposure to smoking, residence and other potential confounding factors (age and sex) that were frequency matched between cases and controls and further adjusted in the analysis. In our study, a significant difference of the *Ku80* G-1401T genotype distribution was found between gastric cancer cases and controls. The frequency of T allele was significantly higher in gastric cancer patients than in control subjects.

The precise mechanisms underlying the relationship between Ku80 polymorphism and stomach carcinogenesis remain unclear. Although the *Ku80* promoter G-1401T genetic variation does not directly lead to amino acid coding change, presumably, it is plausible that this SNP influences the expression level or stability of the Ku80 protein by the alternative spicing, intervention, modification, determination or involvement. It is similar to another important member of NHEJ, XRCC4. A few reports provided evidence that its SNPs located on the promoter region are significant in various cancers[33,34].

Our data also showed that the association between increased gastric cancer risk and the mutant genotypes (GT + TT) was more evident in younger subjects aged < 58 years than in older subjects. We also found an interaction between genotype and sex. The adjusted OR was 1.81 (95% CI: 1.28-2.52) for GT/TT genotype compared with GG genotype among male subjects. But the OR (adjusted OR = 1.33; 95% CI: 0.81-2.24) was not statistically significant among female subjects. Our findings were inconsistent with previous observations by Yang *et al*[17] and Chang *et al*[18]. The reason for the different observations remains unclear.

In addition, we did not note a statistically significant inverse association with gastric cancer risk in both non-smokers (adjusted OR = 1.48; 95% CI: 1.08-2.02) and smokers (adjusted OR = 2.52; 95% CI: 1.25-5.18). But Yang *et al*[17] reported that the GT and TT genotypes, in association with smoking, conferred an increased risk (adjusted OR = 2.537; 95% CI: 1.398-4.601) for colorectal cancer. Similarly, Chang *et al*[18] and Hsu *et al*[19] found a significantly decreased risk of bladder cancer (adjusted OR = 2.053; 95% CI: 1.232-3.419) and oral cancer in smokers with GT or TT genotypes[18,19]. The results are inconsistent with our findings. The reason for the different observations remains unclear. Several studies have reported that smoking is associated with free radical-induced DNA damage and strand breaks[26], and tobacco smoke contains some potential carcinogens including polycyclic aromatic hydrocarbons, tobacco nitro-amines, aromatic amines and BPDE, which form DNA bulky adducts and DNA strand breaks[27,35].

The stratified analyses by residence revealed that the association was significant in variant genotypes in urban subjects (OR = 1.88; 95% CI: 1.26-2.76) but not in rural subjects (adjusted OR = 1.48; 95% CI: 0.99-2.15). The different results may be explained, at least in part, between rural and urban subjects. Environmental factors, including air, soil, diet, occupation and lifestyle, may be responsible for the different observations between rural and urban subjects. It was plausible, considering the better environment in rural areas[36].

The potential limitations of the present study should be stressed. Firstly, in this hospital-based case-control study, we selected controls from individuals with a variety of nonmalignant diseases. These may cause the possibility of selection bias and confound the results. Nevertheless, the frequencies of *Ku80* G-1401T polymorphism variant alleles were similar to those reported in the NCBI Website in the Asian population studies. T allele frequencies of *Ku80* promoter G-1401T are 15.4% in our

control group and 17.4% for Asian population in NCBI. The genotype distribution of controls in our study met Hardy-Weinberg equilibrium conditions. Secondly, the sample size of the present study was relatively small, which may limit the statistical power. Finally, our study was conducted in Chinese population. Caution should be exercised when extrapolating the data to other ethnic groups.

In conclusion, we found a significant difference in the *Ku80* G-1401T polymorphism distribution between the patients with gastric cancer and the control group. The T allele of the *Ku80* G-1401T was found more frequently in patients with gastric cancer and it may be associated with an increased risk of gastric cancer, suggesting that the polymorphism of *Ku80* G-1401T, involved in the gastric tract carcinogenesis, may be a useful marker for primary prevention and anticancer intervention. Further studies are needed to determine the exact nature of this relationship.

COMMENTS

Background

The *Ku80* gene is an important and specific member of NHEJ. Genetic polymorphisms in *Ku80* genes (G-1401T) influence DNA repair capacity and change the predisposition of several cancers, including colorectal, bladder and oral cancer. Whether genetic variants are involved in the risk of gastric cancer in a Chinese population is unknown.

Research frontiers

In this study, the frequency of the *Ku80* G-1401T GT/TT genotypes was significantly higher in the gastric cancer patients than in control subjects. This is the first analysis of the association between genetic predisposition and gastric cancer risk in Chinese population.

Innovations and breakthroughs

The *Ku80* G-1401T polymorphisms may modulate the development of gastric cancer in a Chinese population.

Applications

The *Ku80* G-1401T GT/TT genotypes can be used as biomarkers for selecting patients from the individuals at high risk for gastric cancer in China. Identifying such susceptibility polymorphisms may lead to the development of tests that allow more focused follow-ups of high-risk groups.

Terminology

The *Ku80* gene, also known as XRCC5, is an important and specific member of NHEJ. As an important component of NHEJ, Ku80 and Ku70 form a heterodimer, which acts as a regulatory subunit of the DNA-dependent protein kinase complex DNA-PK by increasing the affinity of the catalytic subunit PRKDC to DNA.

Peer review

The quality of the work and the methodology are sound. The conclusions are appropriate, although it seems unlikely that these findings represent a major breakthrough.

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